Journal of Microbiology, Immunology and Infection (2016) 49, 257–263

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ORIGINAL ARTICLE

Comorbidities of pediatric systemic lupus erythematosus: A 6-year nationwide population-based study

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Received 7 April 2013; received in revised form 14 April 2014; accepted 9 May 2014
Available online 24 July 2014

KEYWORDS
Comorbidity;
Pediatric;
Systemic lupus erythematosus;
Taiwan

Objective: Systemic lupus erythematous (SLE) is a systemic and complex disease that can involve multiple organs. To clarify the risk of developing associated comorbidities after a diagnosis of SLE in children, we used the National Health Insurance Research Database (NHIRD) in Taiwan to investigate diseases experienced in these patients. This is the first nationwide population-based study of the comorbidities of pediatric SLE patients.
Methods: The study was based on data from the NHIRD in Taiwan. Children were enrolled who were below the age of 18 years and whose disease corresponded to the International Classification of Disease, Ninth Revision Clinical Modification (ICD-9-CM) diagnostic code of 710.0 (SLE). The comorbidities associated with SLE were defined by the ICD-9-CM codes of diseases that presented after the SLE diagnosis. We analyzed the common diseases in SLE patients and compared the frequency of these diseases between pediatric SLE patients and the non-SLE population.
Results: From January 1, 2003 to December 31, 2008, we enrolled 904 SLE patients (774 females, 130 males). Infection (86.36%) was the most common comorbidity in pediatric SLE. Other comorbidities were musculoskeletal diseases (16.7%), cardiovascular diseases (16.37%), ocular diseases (10.73%), and renal diseases (6.75%). Children with SLE had a higher

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http://dx.doi.org/10.1016/j.jmii.2014.05.001

risk of heart failure, hypertension, osteoporosis, cataracts, glaucoma, dyslipidemia, seizures, encephalopathy, and malignant changes, compared to non-SLE populations.
Conclusion: The population-based cohort demonstrated several systemic and/or chronic diseases in pediatric SLE patients in Taiwan. Children with SLE were more susceptible to these diseases, including malignancy, compared to the non-SLE population.

Introduction

Systemic lupus erythematosus (SLE) is a complex and chronic autoimmune disease with widely varying clinical manifestations and multiorgan involvement. The disease may present with acute, severe, and life-threatening symptoms, or present as a fluctuating and chronic process that impacts several systems and increases the risk of malignancy.[1,2] In the past decades, the survival of SLE patients has improved in adult and pediatric populations because of increased awareness, early diagnosis, increased availability of immunosuppressants, and improved treatment of associated complications.[3–5] This improvement highlights the importance of treating comorbidities that accompany the disease or its treatment because any treatment should add years to life and add life to years. Furthermore, the known comorbidities that are associated with the disease itself or are a side effect of therapy are independent risk factors for mortality.[6,7] Several population-based studies have been performed on the disease characteristics and comorbidities in adult SLE patients; however, large-scale research in the pediatric population is limited or focuses only on the specific disease.[8–13] Pediatric SLE is different from the adult form, regardless of the clinical manifestation or outcome. Because children with SLE experience more severe disease activity and a longer period of damage accumulation,[14–18] a comprehensive and population-based survey of the comorbidities of pediatric SLE is an issue that urgently needs to be addressed.

Between 2003 and 2008, in an attempt to clarify characteristic comorbidities in children with SLE, we investigated the frequency of associated diseases and evaluated the most common diseases in pediatric SLE patients in Taiwan. We also distinguished the relative risk of these associated diseases in SLE patients, compared to the general population.

Materials and methods

The study was based on data from the National Health Insurance Research Database (NHIRD) in Taiwan. In March 1995, the National Health Insurance (NHI) service was initiated in Taiwan to provide comprehensive medical care to the public. According to the NHI annual statistics report, the coverage rate of NHI in 2007 was nearly 99% of the entire population of Taiwan—more than 25 million people were enrolled in this program. The NHI database consists of the enrollees' integrated information such as demographic data, clinic visits, diagnosis, prescriptions, and hospitalization. The Major Illness/Injury Database is a subpart of the NHIRD, which enrolled people with major and/or chronic diseases such as malignancy or disability. The miserable population applied for a major illness/injury certificate to receive exemption from copayments. Diagnosis and application for a major illness/injury certificate were proposed by clinical physicians, based on the 1997 update of the American College of Rheumatology classification criteria (ACR97; which includes the clinical manifestation and laboratory evidence) for SLE. To assure all enrollees fulfilled accurate diagnostic criteria, the Bureau of the National Health Insurance sifted and validated the applications again with a medical records review that included clinical manifestations, physical examination, and laboratory and image studies. Therefore, the diagnosis of the enrolled patients with SLE was highly accurate and reliable.

We used the International Classification of Disease, Ninth Revision Clinical Modification (ICD-9-CM) codes to define the comorbid diseases. Patients were defined with a systemic or specific disease, if the corresponding ICD-9-CM code presented after SLE and it was repeated at least three times either with outpatient claims or on hospitalization. For the accuracy of diagnosis, all comorbid diagnoses should satisfy ICD-9-CM code criteria and the associated medication. For instance, a diagnosis of urinary tract infection was indeed defined by the corresponding ICD-9 code, which was repeated at least three times, and by the antibiotic treatment. All associated diseases were further divided into subgroups by system or by disease characteristics such as cardiovascular diseases, infection, malignancy, neurological diseases, gastrointestinal diseases, metabolic disease, renal diseases, ocular diseases, and musculoskeletal diseases (Table 1).

From January 1, 2003 to December 31, 2008, patients with SLE were enrolled in the study. The patients with SLE were selected from the Catastrophic Illness Database with the corresponding ICD-9-CM code 710.0 (SLE) and were younger than 18 years of age. All patients were divided into groups by sex. The comorbidities of systemic lupus erythematosus were defined by the ICD-9-CM codes of the diseases that presented after SLE. By excluding the patients with ICD-9-CM codes corresponding to SLE, the non-SLE population was extracted randomly from the general population. Individuals of this population were aged younger than 18 years and without a diagnosis of SLE in the Statistical Yearbook of the Interior (http://sowf.moi.gov.tw/stat/year/list.htm), an official publication of Taiwan's Ministry of the Interior.

Table 1 International Classification of Disease, Ninth Revision Clinical Modification (ICD-9-CM) codes for the comorbidities

Comorbidity	ICD-9-CM codes
Cardiovascular	
Hypertension	401, 402, 404–405
Ischemic heart disease	410–412, 413, 414, 414.0, 414.00, 414.01, 414.04, 414.8, 414.9
Cardiopathy	429, 429.7
Congestive heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 40493, 428
Cerebrovascular diseases	430–437
Peripheral vascular disorders	440, 441.2, 441.4, 441.7, 441.9, 443–444, 447.1
Neurological	
Epilepsy	345, 345.1, 345.4, 345.5, 345.7, 345.8, 345.9
CNS abnormalities	330–331, 331.7, 331.8, 331.89, 331.9, 341, 341.0, 341.8, 341.9
Encephalopathy	348.3, 348.9
Metabolic disease	
Diabetes mellitus	250
Dyslipidemia	272.0–272.4
Hepatic and gastrointestinal	
Autoimmune hepatitis	5714, 571.40, 571.41, 571.49, 571.8, 571.9, 794.8
Gastrointestinal bleeding and ulcer	578, 530–535
Malignancy	
Lymphoma (including non-Hodgkin lymphoma)	200, 202–203
Leukemia	204–208
Solid tumor	140–199
Infection	
Lower respiratory tract infection	480–487, 490
Urinary tract infection	590, 595.9, 597, 599
Musculoskeletal	
Osteopenia	733, 733.0, 733.00, 733.02, 733.09
Avascular necrosis	733.4
Osteoarthritis and arthropathy	715, 716.90, 726.90
Ocular	
Cataract	366, 366.0, 366.17–366.19, 366.3, 366.4, 366.44, 366.8, 366.9
Glaucoma	365
Pulmonary	517.8
Renal	
Renal failure	585, 586

Statistical analysis

We calculated the proportion of comorbidities presenting in the pediatric population and in the adult SLE population. A Chi-square test was used to compare the difference between pediatric SLE patients and non-SLE population in the proportion of comorbidities. The NHI database included nearly 99% of the entire population and represented a nationwide feature: the standard general population. We compared the groups with relative risk. A value of $p < 0.001$ was considered statistically significant. The confidence interval is not reported in this study because the data are from a national population rather than from a sample. For statistical analysis of the data in this study we used SAS statistical package (SAS System for Windows, version 9.0, SAS Institute, Cary, NC, USA) and SPSS software (version 17.0, SPSS Inc., Chicago, Illinois, USA).

Results

During the period from January 1, 2003 to December 31, 2008, a total of 904 SLE patients (774 female, 130 male) were enrolled. The number of patients, based on different age groups at the initial diagnosis, were 4 patients in age group 0–3 years; 16 patients in age group 4–6 years; 44 patients in age group 7–9 years; 120 patients in age group 10–12 years; 270 patients in age group 13–15 years; and 450 patients in age group 16–18 years. Table 2 shows the frequency of comorbidities in the SLE patients and in the general population and the relative risk of each disease between the groups. End-stage renal disease was the highest risk comorbid condition in SLE patients [relative risk (RR), 115.77], compared to the normal populations. Compared to the non-SLE population, patients with SLE had a significantly higher risk of ischemic heart disease (RR, 4.42), heart failure (RR, 13.98), hypertension (RR, 52.31), cerebrovascular disease (RR, 8.28), osteoporosis (RR, 17.96), osteoarthritis and arthropathy (RR, 3.05), cataracts (RR, 18.53), glaucoma (RR, 9.01), dyslipidemia (RR, 12.07), autoimmune hepatitis (RR, 3.53), lymphoma (RR, 22.82), other solid tumors (RR, 4.74), and urinary tract infections (RR, 2.21) ($p < 0.001$ in all patients). Fig. 1 shows the percentage ofSLE patients with comorbidities. Infection (86.36%), musculoskeletal diseases (e.g., osteoporosis and

Table 2 The percentage of comorbid diseases in the pediatric SLE and non-SLE populations and the relative risk between the groups

		SLE patients (n = 904)		Non-SLE patients (n = 5,486,808)		RR	p*
		N	%	*N*	%		
Cardiovascular	Heart failure	15	1.66	6513	0.12	13.98	<0.001
	Cardiopathy	6	0.66	27,075	0.49	1.35	0.47
	Hypertension	112	12.39	12,995	0.24	52.31	<0.001
	Ischemic heart disease	6	0.66	8244	0.15	4.42	<0.001
Cerebrovascular	Cerebrovascular disease	18	1.99	13,192	0.24	8.28	<0.001
Metabolic	Dyslipidemia	61	6.75	30,673	0.56	12.07	<0.001
	Diabetes mellitus	9	1.00	21,213	0.39	2.58	0.003
Renal	Renal failure	61	6.75	3198	0.06	115.77	<0.001
Musculoskeletal	Osteoporosis, including AVN	39	4.31	13,177	0.24	17.96	<0.001
	Osteoarthrosis and arthropathy	96	10.62	191,245	3.49	3.05	<0.001
Gastrointestinal	GI bleeding	11	1.22	24,652	0.45	2.71	0.001
	Autoimmune hepatitis	60	6.64	103,158	1.88	3.53	<0.001
Ophthalmologic	Cataracts	25	2.77	8188	0.15	18.53	<0.001
	Glaucoma	54	5.97	36,365	0.66	9.01	<0.001
Infection	Lower airway infection	297	32.85	2,193,143	39.97	0.82	<0.001
	Urinary tract infection	217	24.00	595,069	10.85	2.21	<0.001
Neurological	CNS abnormality	6	0.66	4826	0.09	7.55	<0.001
	Seizure	15	1.66	16,218	0.30	5.61	<0.001
	Encephalopathy	9	1.00	11,488	0.21	4.75	<0.001
Malignancy	Lymphoma (including NHL)	6	0.66	1596	0.03	22.82	<0.001
	Other solid tumors	14	1.55	17,935	0.33	4.74	<0.001

* $p < 0.001$ indicates statistical significance.
AVN = avascular necrosis; CNS = central nervous system; GI = gastrointestinal; NHL = non-Hodgkin lymphoma; RR = relative risk; SLE = systemic lupus erythematosus.

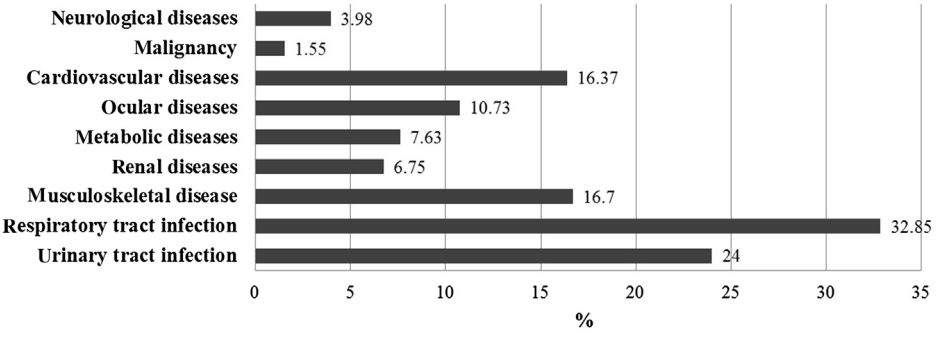

Figure 1. The percentage of comorbidities in pediatric SLE patients. Using the International Classification of Disease, Ninth Revision Clinical Modification (ICD-9-CM) codes, diseases that presented after the diagnosis of SLE were identified. All associated diseases were further divided into subgroups by system or by disease characteristics such as cardiovascular diseases, infection, malignancy, neurological diseases, gastrointestinal diseases, metabolic disease, renal diseases, ocular diseases, and musculoskeletal diseases (Table 1). Patients were classified into the group of systemic disease or specific disease, if they met any ICD-9-CM code in these categories. Neurological diseases include abnormalities of the central nervous system, seizures and encephalopathy; malignancy includes lymphoma, non-Hodgkin lymphoma, and other solid tumors; cardiovascular diseases include heart failure, ischemic heart disease, cardiopathy, and hypertension; gastrointestinal diseases include gastrointestinal bleeding and autoimmune hepatitis; ocular diseases include cataracts and glaucoma; metabolic diseases include dyslipidemia and diabetes mellitus; renal diseases include end-stage renal disease; musculoskeletal diseases include osteoporosis, avascular necrosis, osteoarthritis, and arthropathy; infection includes lower respiratory tract infection and urinary tract infection. SLE = systemic lupus erythematosus.

avascular necrosis; 16.70%), cardiovascular diseases (16.37%), ocular diseases (e.g., cataracts and glaucoma; 10.73%), metabolic diseases (7.63%), and renal diseases (6.75%) were the leading comorbidities that impacted all children with SLE.

Discussion

The present study is the first nationwide population-based study on the comorbidities of pediatric SLE patients. We identified the proportion affected and the relative risks of comorbidities in pediatric SLE patients in Taiwan.

Despite improvements in treatment strategies, infection remains the leading disease associated with SLE patients in Taiwan, in particular urinary tract infection.[19–22] However, lower respiratory tract infections in the SLE patients in this cohort seemed to achieve favorable outcomes, compared to the outcome of the non-SLE population. This may be attributed to the decreased prevalence of lupus, but higher incidence of viral bronchiolitis, viral pneumonitis, or atypical pneumonia at a young age.

Apart from infection, the comorbidities in SLE children most frequently involved cardiovascular diseases (28.54%), musculoskeletal diseases (16.7%), ocular diseases (10.73%), metabolic diseases (7.63%), and renal diseases (6.75%). Any underlying damage may result from the nature of SLE or could result from the medical intervention. Corresponding to our disease domain, we reviewed the literature reporting comorbidities in children with SLE. Several small-sized studies have previously focused on the comorbidities in children with SLE.

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index score (SDI) was the primary outcome measure of the accumulated and irreversible damage that results from disease activity and from the adverse effects of medications. It has been validated as an instrument for documenting SLE-associated morbidity in adult patients and in pediatric patients.[23–25] The SDI assesses 12 organ systems with scores ranging from 0 to 47. The definition of damage index includes specific disease severity and duration. In some chronic and comparatively steady conditions such as cataracts, end-stage renal disease, avascular necrosis, or osteoporosis, the damage index may correspond to our disease classification.

Brunner et al[14] retrospectively investigated disease activity and damage in 66 patients with a mean follow up of 3.3 years (3.3 $\pm$ 2.0 years). They found that damage occurred primarily in the ocular system (43.9%), musculoskeletal system (25.7%), neuropsychiatric system (10.6), and renal system (9.0%).

Similar findings were documented in a multicenter, multinational study with a longer follow-up period (mean follow up, 5.0 $\pm$ 3.6 years). Ravelli et al[18] determined the accumulated damage in 387 patients enrolled in a European pediatric rheumatology center. Damage to the renal system (21.8%) exceeded other problems and was followed by damage to the neuropsychiatric domain (15.8%), musculoskeletal domain (11.7%), and ocular domain (10.9%).

In 2006, Bandeira et al[23] focused on the relationship between damage accrual, disease flares, and cumulative drug therapies in juvenile-onset SLE. In this study, 57 patients were followed prospectively in three tertiary centers for 3 years or more. Damage accrual was significant in the ocular domain (12.3%) and renal domain (12.3%). With slight differences in the proportions, a cross-sectional study of 181 patients with a mean follow up of 3 years also found that the most frequent areas of damage were in the renal domain (13%), neuropsychiatric domain (10.7%), musculoskeletal domain (10.7%), ocular domain (8.2%), and skin domain (7.6%). Some instances of renal disease such as an acute stage of glomerulonephritis or nephrotic syndrome may have a limited presentation at the initial diagnosis or acute flare up because renal involvement is a diagnostic criterion and is the most common manifestation in juvenile-onset SLE. Thus, we defined the associated diseases as limited to the chronic state and their ICD-9 codes should be repeated more than twice either in an outpatient department or on hospitalization. Since the early 1990s, when pulse cyclophosphamide therapy was introduced for treating lupus nephritis, the incidence of end-stage renal disease secondary to lupus has dropped significantly. The percentage of renal failure (i.e., end-stage renal disease) in our cohort was 6.75%, which is consistent with previous studies.[22,26] We demonstrated that the levels of permanent renal damage and end-stage renal disease were similar to the levels in the general population in developed countries.

Furthermore, hypertension was present in 12.39% of our pediatric SLE patients. Hypertension is an independent risk factor for the progression of renal diseases and often develops in the pediatric SLE population because of premature atherosclerosis resulting from renal disease, chronic inflammation, and prolonged steroid use, as described in previous reports.[26–30]

A population-based study showed that adult SLE patients have a higher risk of malignant change, whether the malignancies were hematological (e.g., non-Hodgkin's lymphoma) or solid tumors,[31] and a similar phenomenon occurred in different ethnic groups, which constituted our cohort.[32–35] The mechanism linking malignancies and SLE remains unclear. An increase in malignancies may result from the inflammatory nature of lupus or from the immunosuppressive treatments for SLE. The results of the present nationwide study were consistent with the involvement of some domains in a serial literature review and demonstrate the clinical risk of several systemic diseases that occur in children with SLE.

Neuropsychiatric disease was likely to be underestimated because limited information was available concerning neuropsychiatric disease without a detailed chart review. For instance, without detailed chart reviews, it can be difficult to differentiate cognitive impairment associated with lupus from an undocumented underlying developmental problem.

Compared with the non-SLE population, children with SLE had a relatively higher risk of several systemic diseases such as hypertension, heart failure, dyslipidemia, renal failure, osteoporosis and avascular necrosis, autoimmune hepatitis, cataracts, glaucoma, urinary tract infections, central nervous system abnormalities, seizures, encephalopathy, and lymphoma, all of which were statistically significant ($p < 0.001$). The susceptibility to diseases may be influenced by several intrinsic and acquired etiologies related to lupus itself, or related to commonly used

immunosuppressive therapies. Because of the limitations of the information obtained from the database, we were unable to acquire accurate data regarding the age at disease onset, family history, disease activity, and the cumulative dose of the immunosuppressant therapy to clarify such relationships. The current study only showed the correlation and relative risk between diseases, but not a causal relation. Another limitation is that the follow-up period could not be defined clearly. Further study to clarify the onset of SLE disease and its comorbidities is necessary. The clinical significance of this study is to remind physicians of the development of possible comorbid conditions when following up with SLE patients. Because the comorbidities impact the quality of life and are a risk factor for mortality, recognizing the association between damage accumulation, medical intervention, and the timing of the occurrences of comorbidities is an important issue.

The present cohort is the first nationwide population-based study on the comorbidities of pediatric SLE. We demonstrated that characteristic diseases are associated with SLE in the pediatric population. The leading comorbidities of children with SLE in Taiwan are infection, renal diseases, musculoskeletal diseases, cardiovascular diseases, and ocular diseases. Compared to the non-SLE population, children with SLE were more susceptible to these diseases, even malignancy.

Conflicts of interest

The authors do not have any financial support or other benefits from commercial sources for the work reported in the manuscript. They also do not have any other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with regard to this work.

References

1. Barron KS, Silverman ED, Gonzales J, Reveille JD. Clinical, serologic, and immunogenetic studies in childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 1993;**36**:348—54.
2. Hay E, Gordon C, Emery P. Assessment of lupus: where are we now? *Ann Rheum Dis* 1993;**52**:169—72.
3. Urowitz MB, Gladman DD, Tom BD, Ibañez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. *J Rheumatol* 2008;**35**:2152—8.
4. Hashkes PJ, Wright BM, Lauer MS, Worley SE, Tang AS, Roettcher PA, et al. Mortality outcomes in pediatric rheumatology in the US. *Arthritis Rheum* 2010;**62**:599—608.
5. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al., European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period, a comparison of early and late manifestation in a cohort of 1000 patients. *Medicine* 2003;**82**:299—308.
6. Ruperto N, Buratti S, Duarte-Salazar C, Pistorio A, Reiff A, Bernstein B, et al. Health-related quality of life in juvenile-onset systemic lupus erythematosus and its relationship to disease activity and damage. *Arthritis Rheum* 2004;**51**:458—64.
7. Rahman P, Gladman DD, Urowitz MB, Hallett D, Tam LS. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. *Lupus* 2001;**10**:93—6.
8. Voss A, Green A, Junker P. Systemic lupus erythematosus in Denmark: clinical and epidemiological characterization of a county-based cohort. *Scand J Rheumatol* 1998;**27**:98—105.
9. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. *J Rheumatol* 2000;**27**:1884—91.
10. Molina MJ, Mayor AM, Franco AE, Morell CA, López MA, Vilá LM, et al. Prevalence of systemic lupus erythematosus and associated comorbidities in Puerto Rico. *J Clin Rheumatol* 2007;**13**:202—4.
11. Laustrup H, Voss A, Green A, Junker P. SLE disease pattern in a Danish population-based lupus cohort: an 8-year prospective study. *Lupus* 2010;**19**:239—46.
12. Chiu TM, Lai CH. Nationwide population-based epidemiologic study of systemic lupus erythematosus in Taiwan. *Lupus* 2010;**19**:1250—5.
13. Björnådal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: result from a Swedish population based study 1964—95. *J Rheumatol* 2004;**31**:713—9.
14. Brunner HI, Silverman ED, To T, Bombardier C, Feldman BM. Risk factor for damage in childhood-onset systemic lupus erythematosus, cumulative disease activity and medication use predict disease damage. *Arthritis Rheum* 2002;**46**:436—44.
15. Ravelli A, Ruperto N, Martini A. Outcome in juvenile onset systemic lupus erythematosus. *Curr Opin Rheumatol* 2005;**17**:568—73.
16. Gutiérrez-Suárez R, Ruperto N, Gastaldi R, Pistorio A, Felici E, Burgos-Vargas R, et al. A proposal for a pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index based on the analysis of 1,015 patients with juvenile-onset systemic lupus erythematosus. *Arthritis Rheum* 2006;**54**:2989—96.
17. Mina R, Brunner H. Pediatric lupus—are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? *Rheum Dis Clin N Am* 2010;**36**:53—80.
18. Ravelli A, Duarte-Salazar C, Buratti S, Reiff A, Bernstein B, Maldonado-Velazquez MR, et al. Assessment of damage in juvenile-onset systemic lupus erythematosus: a multicenter cohort study. *Arthritis Rheum* 2003;**49**:501—7.
19. Huang JL, Lin CJ, Hung IJ, Luo SF. The morbidity and mortality associated with childhood onset systemic lupus erythematosus. *Chang Gung Med J* 1994;**17**:113—20.
20. Wang LC, Yang YH, Lu MY, Chiang BL. Retrospective analysis of mortality and morbidity of pediatric systemic lupus erythematosus in the past two decades. *J Microbiol Immunol Infect* 2003;**36**:203—8.
21. Huang JL, Yeh KW, Yao TC, Huang YL, Chung HT, Ou LS, et al. Pediatric lupus in Asia. *Lupus* 2010;**19**:1414—8.
22. Wang LC, Yang YH, Lu MY, Chiang BL. Retrospective analysis of the renal outcome of pediatric lupus nephritis. *Clin Rheumatol* 2004;**23**:318—23.
23. Bandeira M, Buratti S, Bartoli M, Gasparini C, Breda L, Martini A, et al. Relationship between damage accrual, disease flares and cumulative drug therapies in juvenile-onset systemic lupus erythematosus. *Lupus* 2006;**15**:515—20.
24. Hiraki LT, Hamilton J, Silverman ED. Measuring permanent damage in pediatric systemic lupus erythematosus. *Lupus* 2007;**16**:657—62.
25. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;**39**:363—9.

26. Bogdanović R, Nikolić V, Pasić S, Dimitrijević J, Lipkovska-Marković J, Erić-Marinković J, et al. Lupus nephritis in childhood: a review of 53 patients followed at single center. *Pediatr Nephrol* 2004;**19**:36—44.
27. de Leeuw K, Smit AJ, de Groot E, van Roon AM, Kallenberg CG, Bijl M, et al. Longitudinal study on premature atherosclerosis in patients with systemic lupus erythematosus. *Atherosclerosis* 2009;**206**:546—50.
28. Schanberg LE, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, et al., Atherosclerosis Prevention in Pediatric Lupus Erythematosus Investigators. Premature atherosclerosis in pediatric systemic lupus erythematosus: risk factors for increased carotid intima—media thickness in the atherosclerosis prevention in pediatric lupus erythematosus cohort. *Arthritis Rheum* 2009;**60**:1496—507.
29. Sabio JM, Vargas-Hitos J, Zamora-Pasadas M, Mediavilla JD, Navarrete N, Ramirez A, et al., Grupo Lupus Virgen de las Nieves. Metabolic syndrome is associated with increased arterial stiffness and biomarkers of subclinical atherosclerosis in patients with systemic lupus erythematosus. *J Rheumatol* 2009;**36**:2204—11.
30. Tyrrell PN, Beyene J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ, et al. Rheumatic disease and carotid intima—media thickness, a systemic review and meta-analysis. *Arterioscler Thromb Vasc Biol* 2010;**30**:1014—26.
31. Chen YJ, Chang YT, Wang CB, Wu CY. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. *Am J Med* 2010;**123**:1150e1—6.
32. Löfström B, Backlin C, Sundström C, Ekbom A, Lundberg IE. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. *Ann Rheum Dis* 2007;**66**:1627—32.
33. Bernatsky S, Joseph L, Boivin JF, Gordon C, Urowitz M, Gladman D, et al. The relationship between cancer and medication exposures in systemic lupus erythematosus: a case-cohort study. *Ann Rheum Dis* 2008;**67**:74—9.
34. Gayed M, Bernatsky S, Ramsey-Goldman R, Clarke A, Gordon C. Lupus and cancer. *Lupus* 2009;**18**:479—85.
35. Kiss E, Kovacs L, Szodoray P. Malignancies in systemic lupus erythematosus. *Autoimmun Rev* 2010;**9**:195—9.